REMARKS

A. Introduction

The Examiner has once again rejected Applicant's arguments regarding this case, which leaves Applicant confused. After two separate interviews it appeared the Examiner suggested claim amendments that would place this case in a position for allowance, and each time the amendments were made the Examiner rejected the claims on the same grounds as before. The Examiner has refused to accept the logic behind Applicant's arguments or to accept Applicant's explanation for why the 103 rejections are improper. It appears as though Examiner doesn't understand this invention or the references being cited against this invention in a way sufficient to defend the rejections, yet they continue to be maintained. Applicant contends that the arguments made in the last 4 responses are sufficient to overcome the rejections, and therefore intends to appeal this final rejection unless Examiner is willing to address the prior office action in a way that is consistent with the interviews and Applicant's own understanding of this invention.

Applicant respectfully draws the Examiner's attention to several specific points in the last Office Action as examples of the Examiner's apparent failure to understand the invention or the cited references. Specifically, on p. 6 the Examiner states:

The specification does not teach a positive signal is generated. The specification does teach that "a" signal is detected with the presence of both labels or the presence of a third color created by the juxtaposition of the two or three labels. However, the specification does not teach that the signal that is generate (sic) only when two or more components are co-localized is positive. Furthermore, the specification teaches that the label can be fluorescent and detected by fluorescence measurement (see pg 18, lines 5-9). Detection by fluorescence encompasses both positive and negative signals, for example detection of a fluorescence signal can encompass quenching of the signal, thereby detecting a negative signal. The support in the specification teaches a signal is generated when the presence of two or three components of RecA and MutS; probe DNA and MutS; or RecA, MutS and probe DNA is co-localized (see page 17, lines 3-5 and pg. 19, lines 3-9 or paragraphs 103 and 113 of the published application), however the specification does not provide support for co-localization of two "or more" components nor teach that a positive signal is generated "only" when two or more components are co-localized.

The quotation above is provided to illustrate the Examiner's apparent lack of scientific knowledge in this area as a "quenched" signal or a "negative" signal cannot be detected. Applicant

points out that the "quenching" of a signal causes it not to be non-detectable as "quenching" of a signal causes the loss of that particular signal. The present invention provides detection of a signal that is generated when the presence of two or three components of RecA and MutS; probe DNA and MutS; or RecA, MutS and probe DNA are co-localized. The invention is not concerned with those things that do not generate a signal as the lack of a signal is indicative of the absence of the two or three components of interest being co-localized. The present invention is concerned with the co-localization of these components as that is indicative of a SNP. That is why the present invention teaches the labeling of MutS, RecA or SSB proteins, for example, in order to detect the two or three components of interest (paragraph [0107] published application).

Applicant also directs the Examiner's attention to the 5th sentence in the first full paragraph on p. 20 wherein she states, "[i]t is noted that the examiner was not asserting that MutS is a single-stranded binding protein." This is in direct contrast to her statement in a previous office action wherein she stated, "... MutS is a single stranded binding protein." (Advisory Action mailed January 18, 2007 p. 4, line 2). Applicant is frankly quite confused what the Examiner thinks about RecA and MutS as she appears to be changing her mind from office action to office action.

Applicant also directs the Examiner's attention to the sentence at the top of p. 14 of the present office action wherein she states, "[t]here is no teaching by Wagner et al. that MutS cannot bind a DNA triplex and therefore there is a reasonable expectation of success that MutS would bind triplex structures." Applicant is absolutely shocked that the Examiner appears to feel that the fact that something is not known to behave in a particular way is actually supporting evidence that it does do the very thing that it is not known to do. This makes absolutely no scientific or legal sense to the Applicant.

For the sake of convenience, Applicant's last response is included in its entirety below. Applicant also includes the Declaration filed with the last response hereto.

B. Response Filed October 29, 2007

1. Rejection of Claim 69 under 35 U.S.C. 112, second paragraph

The Examiner has rejected claim 69 under 35 U.S.C. 112, second paragraph, for the reasons of record.

In response to the Examiner's argument, and in order to expedite allowance of claims, Applicants have cancelled claim 69. Such cancellation is made without prejudice or disclaimer of the subject matter therein and solely in order to expedite prosecution and allowance of the claims. In light of the aforementioned cancellation, Applicants respectfully request withdrawal of the rejection of claim 69 under 35 U.S.C 112, second paragraph.

2. Common Ownership

The Examiner is thanked for reminding Applicants of their obligation to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made. Applicants assert that all claims were commonly owned at the time a later invention was made.

3. Rejection of Claims 56-68 and 70-75 under 35 U.S.C. 103(a)

Claims 56-68 and 70-75 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kigawa et al. in view of Wagner et al. for the reasons of record.

Initially, Applicants would like to point out that to establish a prima facie case of obviousness, it must be shown that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson,* 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Applicants respectfully submit that the Examiner has not met this burden. Specifically, instant claim 56 contains a limitation to the generation of a positive signal only when two or more components are co-localized, thus allowing detection without removal of unreacted probes. In contrast, the references cited by the Examiner are silent with respect to generating a positive signal only when two or more components are co-localized. Thus, each and every limitation of claim 56 is not taught or suggested by the prior art references.

The examiner states on Page 4 of the outstanding action that, "Kigawa et al. does not teach the use of MutS protein with RecA for the detection of single nucleotide base pair insertions, deletions or polymorphisms." Applicants submit that Kigawa does not teach the use of RecA for the detection of single nucleotide base pair of anything. The portion of Kigawa identified by the Examiner to support the assertion that Kigawa teaches the detection of deletions and insertions

(column 13, lines 18-21) is misplaced. Rather, this portion of Kigawa is directed to a discussion of changes in ploidy (i.e., the gain or loss of an **entire** chromosome) and teaches detection of genetic alterations by means of fluorescent microscopic — detection of changes in separation of two probes complementary to nearby regions of the chromosome. As such, detection of a change as taught or suggested by Kigawa would require a very large insertion or deletion, or a large inversion or translocation. Single base pair insertions or deletions could **never** be detected in the system taught by Kigawa.

Further, Kigawa et al. teaches away from co-localized signal generation. In certain embodiments of the instant invention, the probe and test DNA that together form a D loop must have sequence differences that result in formation of mispaired or unpaired bases in a probe/test duplex region. In contrast, Kigawa et al. teaches removing part of the probe/RecA complex that has not been coupled to the double-stranded target nucleic acid sequence. (See column 4, lines 25-27; column 9, lines 22-24; column 9, lines 63-64; and elsewhere). As such, even if one of ordinary skill in the art were to combine Kigawa with Wagner as suggested by the Examiner, the combination would not yield the instant invention.

To suggest that Wagner et al. teaches that MutS can recognize mismatches in DNA triplexes, when there are no data to support such a suggestion, is misplaced as well.. The notion that binding to one kind of triplex suggests that all triplexes can be recognized also lacks support in the outstanding action and in the art. Without being bound to any particular theory, Applicants suggest that not all duplexes can be recognized (i.e., DNA/RNA duplexes are not recognized by E. coli MutS). (*See* Declaration submitted herewith). Furthermore, in vivo data suggest that MutS does not bind RNA duplexes containing mispaired or unpaired bases, such as tRNA. (*Id.*).

When an independent claim is deemed nonobvious under 35 USC 103, then all claims depending therefrom are nonobvious as well. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed Cir. 1988). Applicants assert that in light of the foregoing arguments, dependent claims 57-68 and 70-75 are allowable for the same reasons as independent claim 56.

Thus, Applicants respectfully request withdrawal of the rejection of claims 56-68 and 70-75 under 35 U.S.C. 103(a).

Maintained Rejections

4. Rejection of Claims 56-68 and 70-75 under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 56-68 and 70-75 under 35 U.S.C. 112, first paragraph for the reasons of record. Specifically, the Examiner argued that the recitation of Claim 56 "wherein a positive signal is generated only when two or more components are co-localized, thus allowing detection" is not supported by the Specification. Applicants respectfully traverse this rejection.

At the outset, it seems that the Examiner has not reviewed the correct specification in maintaining the instant rejection. The Examiner stated that in the specification of Patent Application Publication No. US2004/0224336A1 there appears no reference of the cited paragraph numbers for support of the claims. However, Applicants assert Patent Application Publication No. US2004/0224336A1 corresponds to Application Serial No. 10/792,785. As such, it seems that the Examiner has not reviewed the correct specification. The instant Office Action pertains to Application Serial No. 10/078,278, not Application Serial No. 10/792,785. Thus, Applicants respectfully request the Examiner to review Applicants' comments that follow in light of the specification in Patent Application Serial No. 10/078,278.

Applicants respectfully direct the Examiner to paragraph [0046] of the Specification wherein it states, "[i]n the methods described herein, detection is based on the use any one of the components detectably labeled: the probe DNA, the RecA, the MutS, (or SSB, discussed below). The label may be any suitable detectable label, e.g., a fluorophore, a chromophore, a radionuclide, biotin, digoxigenin, etc."

Applicants further direct the Examiner to paragraph [0103] of the published application wherein the Specification states, "[i]n this method detection of mutations and SNPs is accomplished by detecting the co-localization of either (a) RecA and MutS, (b) probe DNA and MutS or (c) RecA, MutS and probe DNA."

Applicants also direct the Examiner to paragraph [0113] wherein the Specification states, "[t]he flow cytometer is set to detect as a signal the ***simultaneous*** presence of both labels (that on the MutS and that on the RecA and/or probe) or the presence of a 'third' color created by the juxtaposition of the two (or three) labels. The presence of such signals is an indication of the presence in the sample of sequences differing from the probe by one or a few single mismatches or unpaired bases." ***(emphasis added)***

Applicants next direct the Examiner to paragraph [0114] wherein the Specification states, "[t]he power of the RecA/MutS method described herein is that the background signals are very low, and RecA+MutS (or MutS+DNA probe or MutS+RecA+DNA probe) will be found together only

under conditions in which RecA-coated oligonucleotide probe has bound to test DNA in a way that creates a heteroduplex with a mismatched or unpaired base."

Applicants further direct the Examiner to paragraph [0118] wherein the Specification states, "[i]n another generally applicable embodiment of this invention, MutS may be immobilized, and either the probe of the RecA may be detectably labeled. In this embodiment, binding of the probe or RecA to immobilized MutS is indicative of one or more mismatches or unpaired bases in the D-loop structure formed between the probe and test DNA."

The Examiner is next directed to paragraph [0069] wherein Figures 1-7 are described and the Specification states,

> FIGS. 1-7 are schematic representations of the RecA+MutS mutation/SNP detection method including various detection modalities." In particular, paragraph [0070] of Figure 1 depicts the general concept of the invention wherein it states that, "an oligonucleotide "probe" to which is added in Step (1) the RecA (smallcircle) protein. RecA coats the probe to form a "RecA filament." In Step (2) RecA filament is added to test DNA and allowed to form a triple stranded or "D-loop" structure. In Step (3), the MutS protein is added. If the probe is identical to the test DNA sequence, a perfectly paired duplex ("no mismatch") is formed and the MutS does not bind (left). If there are one or more sequence differences between the probe and test DNA sequences, a heteroduplex is formed containing one or more mismatches or unpaired bases ("Mismatch (SNP)") and MutS binds to that heteroduplex.

Throughout the Specification, specific detection methods in a variety of different embodiments are described in detail. For instance, flow cytometry is described in paragraphs [0113] to [0116], standard genotyping is described in paragraph [0123], a variety of other methods that utilize the formation of heteroduplex DNA [0127], and the like. Unreacted components in the reaction mix are not scored and independent claim 56 includes the claim limitation, "wherein a positive signal is generated only when two or more components are co-localized, thus allowing detection."

As such, the Specification clearly teaches that one of the components must be labeled (herein probe DNA, RecA, MutS or SSB) and that subsequent detection is dependent on the "co-localization" of two or more components (herein RecA and MutS, probe DNA and MutS or RecA, MutS and probe DNA) and the Specification teaches the detection of those two or more components.

In light of the foregoing, one skilled in the art would realize that a positive signal is generated when there is co-localization of two or more components of the present invention with one such component being labeled. More specifically, the co-localization of RecA and/or probe DNA with MutS is a feature of the present invention and the labeling of one or more of these three components allows for the detection of such co-localized components.

Accordingly, Applicants submit that the specification describes the claimed invention in such a way as to convey to one of skill in the art that the Applicants had possession of the claimed invention consistent with 35 U.S.C. 112, first paragraph and relevant case law. (Lockwood v. American Airlines, Inc. 107 F. 3d 1565, 41 USPQ2d 1061 (Fed Cir. 1997); and In re Gostelli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989)). As such, Applicants respectfully request withdrawal of the Examiner's rejection of Claims 56-68 and 70-75 under 35 U.S.C. 112, first paragraph.

5. Rejection of Claims 56-68 and 70-75 under 35 U.S.C. 103(a)

The Examiner has rejected claims 56-68 and 70-75 under 35 U.S.C. 103(a) as being unpatentable over Kigawa et al. in view of Nolan et al. for the reasons of record. Applicants respectfully traverse this rejection.

Initially, Applicants would like to point out that to establish a prima facie case of obviousness, it must be shown that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson,* 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Applicants respectfully submit that the Examiner has not met this burden. Specifically, instant claim 56 contains a limitation to the generation of a positive signal only when two or more components are co-localized, thus allowing detection without removal of unreacted probes. In contrast, the references cited by the Examiner are silent with respect to generating a positive signal only when two or more components are co-localized. Thus, each and every limtation of claim 56 is not taught or suggested by the cited prior art references.

Further, Kigawa et al. teaches away from co-localized signal generation. In certain embodiments of the instant invention, the probe and test DNA that together form a D loop must have sequence differences that result in formation of mispaired or unpaired bases in a probe/test duplex region. In contrast, Kigawa et al. teaches removing part of the probe/RecA complex that has not been coupled to the double-stranded target nucleic acid sequence. (See column 4, lines 25-27;

column 9, lines 22-24; column 9, lines 63-64; and elsewhere). Furthermore, Kigawa et al. teach that it is undesirable to use a wash that contains proteolytic enzymes or protein denaturing surfactants so as not to remove the RecA from the D-loop. (*See* column 9, lines 22-24). Without being bound by any particular theory, Applicants submit that in all other known applications of RecA where the RecA remains bound to the D-loop, further enzymatic action on that DNA is inhibited (e.g., via restriction endonuclease action, DNA methylase action, or DNA ligase action). (*See* Declaration submitted herewith). There is, therefore, every reason to expect that MutS would not be able to recognize mismatches in a RecA coated duplex or in the RecA coated D-loops as taught by Kigawa et al.

The Examiner also points to Kigawa et al. to support the notion that it is known to use single stranded binding proteins to accelerate a reaction. While this is an interesting point, it is misplaced in the instant case in that MutS is not a single stranded binding protein. MutS is a mismatch binding protein and requires double stranded DNA to form a mismatch. Accordingly, Kigawa fails to teach or suggest this aspect of the instant claims. As such, even if one of ordinary skill in the art were to combine Kigawa with Nolan as suggested by the Examiner, the combination would not yield the instant invention.

When an independent claim is deemed nonobvious under 35 USC 103, then all claims depending therefrom are nonobvious as well. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed Cir. 1988). Applicants assert that in light of the foregoing arguments, dependent claims 57-68 and 70-75 are allowable for the same reasons as independent claim 56.

Thus, Applicants respectfully request withdrawal of the rejection of claims 56-68 and 70-75 under 35 U.S.C. 103(a).

3. Concluding Remarks

In view of the foregoing, Applicant respectfully submits that all rejections of record have been overcome. Accordingly, Applicant believes that all currently pending claims are in condition for allowance.

Respectfully Submitted,

3/31/08
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